

FLOUR DUST

CAS number: None

Sensitizer (SEN)

TLVBTWA, 0.5 mg/m³, as inhalable particulate

1999: *Proposed*: TLVBTWA, 0.5 mg/m³, inhalable particulate; Sensitizer (SEN)

2000: TLVBTWA, 0.5 mg/m³, inhalable particulate; SEN

Chemical and Physical Characteristics

Flour is a complex organic dust consisting of wheat, rye, millet, barley, oats, or corn cereals, or a combination of these, which have been processed or ground by milling. Wheat and rye are the two most common grains used to make flour, but they can also be made from beans, peas, chick peas, fruits, or nuts.⁽¹⁾ Flours vary in weight, compressibility, and moisture content. The typical composition of an 85% extraction wheat flour (used for bread making) is 14% protein, 2% oil, 1% cellulose, and 81% non-nitrogenous materials. Wheat is the primary cereal used in bread making; seeds are composed of 85% endosperm, 2% embryo or germ, and 13% husk (bran). Seeds are ground to produce flour, which consists mainly of starch and between 7% and 15% protein. Proteins occur in four groups: 15% water-soluble albumins, 7.5% globulins, 32.5% prolamins (gliadin), and 45% glutelins (glutenin). The last two groups interact in the presence of water to form a viscous complex called gluten, which plays the major role in the structure and texture of bread.⁽²⁾

Wheat is composed of a germ and starch and gluten cells, which are enclosed by fibrous coats. Milling removes the nondigestible bran coats and the germ and reduces the remaining starch and gluten to a fine powder.⁽³⁾ The object of the milling process is to 1) separate the endosperm (required for flour) from bran and germ and 2) reduce the endosperm to the required fineness. The first stage splits the grain, which allows the bran and germ to be separated. Selected parts are then further crushed and separated. The quality of the flour produced depends on 1) the hardness of the wheat (adhesion between starch and protein), 2) strength of the wheat (ability to produce large volume, good crumb texture) which correlates with protein content, 3) particle size distribution, 4) amount of damaged starch, 5) water absorption capacity, and

6) enzyme activity. By blending flours of different hardness and strength, it is possible to change the characteristics of the final mixture. A process involving air classification also allows modification of flour properties as it separates out the heavier particles by projecting the flour in a stream of air and applying a centrifugal force.⁽²⁾

A variety of other materials may be added to flours:

1. Materials used in small quantities to enhance the basic properties, including raising agents, emulsifiers, improvers (alpha-amylase is one example), and artificial sweeteners.
2. Ingredients used to give additional features, such as colors, flavors, raisins, and nuts.
3. Potential ingredients added occasionally for specific effects, such as gums and gelling agents.⁽²⁾

Wheat flour contains small amounts of naturally-occurring alpha-amylase, ranging from 0.1 to 1.0 mg/g flour.^(4,5) Alpha-amylase is a dough improver added to break up the large polysaccharide chains and speed yeast activity. Alpha-amylase is most often derived from fungal organisms such as *Aspergillus oryzae* or *Aspergillus niger*.

Industrial Uses of Flour

Flour is used to make foods for human or animal consumption. Wheat and wheat flour are the primary inputs for the milling and baking industries in the United States. The outer kernel portions of grain are used as millfeeds for livestock; the endosperm is processed into flour. In 1987, there were 211 wheat flour mills producing 338 million cleaned-weight tons (all foreign matter removed) of flour. Roughly 92% of this flour was used domestically, with the remainder being exported. Approximately 15% of domestic flour was sold directly to consumers (as packaged flour and bakery mixes) and the remaining 85% was

processed into bakery items (breads, cakes, cookies, pastas). Flour was also used in breakfast cereals, soups, gravies, and other prepared foods. In 1982, there were approximately 2700 wholesale baking plants in the U.S. (most of the latter employing fewer than 20 workers).⁽⁶⁾

In 1996, 2.3 million bushels of wheat were produced in the U.S. Forty percent of this wheat went into food production, 5% to seed, 13% to feed production, and the remainder was exported.⁽⁷⁾

Sources of Flour Exposure

Exposures to flour occur in milling operations, where grain is processed into flour, and in baking operations, where flour is used to produce a variety of food products. Workers are primarily exposed to flour dust during flour milling and packing operations and while working as bakers or pastry makers. In addition, one study has indicated that farm animal feeders may be exposed during the handling of animal feeds composed primarily of cereal flours.⁽⁸⁾

Flour milling involves the processing and grinding of cereals into flour. Milling has become increasingly industrialized; modern mills contain wholly automated processes controlled from a central area. In these mills, flour is moved throughout the process by pneumatic conveyors. The processing stages include: 1) receiving and discharging grain from ships, railcars, or trucks via hand or automatic methods; 2) storage in grain silos; 3) hoppering, weighing, and cleaning; 4) milling to different particle sizes and separation of by-products for animal food stocks; 5) storage in flour silos and addition of additives; 6) packing in silos, bulk containers, or bags; and 7) transfer to delivery vehicles.⁽¹⁾ Significant grain and flour exposures can occur during any unautomated and non-enclosed portions of the process, especially during receiving, packaging, and final transfer. Maintenance personnel may also experience high exposures when working with process equipment.

Bakeries and biscuit-, pastry-, and cake-making processes all involve flour exposures. Small-scale bakeries are primarily involved in bread making, which occurs in three stages. Flour, water, salt, and yeast are first mixed together to make dough (mixing stage), usually with mechanical mixing machines. The dough is then left to rise in a warm, humid atmosphere (fermentation stage), after which it is divided, weighed, molded, and baked (baking stage). Bread is charged into the oven on paddles or trays; water vapor is given off as steam during the baking.⁽⁹⁾ Exposure levels have been found to be highest during mixing and baking.^(4,5,10,11) Employees in smaller bakeries are often

responsible for carrying out the tasks associated with all of these stages.

Larger industrial bakeries are highly automated. Employees often work in one area and perform tasks associated with only one stage of the process. Machines may perform many of the manual tasks (e.g., beating, kneading) encountered in smaller bakeries. In addition to flour, a variety of other raw materials (including sugar, spices, fruits, and nuts) may be used in industrial bakeries that produce such items as pastries, biscuits and cakes. Exposures to flour in larger bakeries, regardless of the product, can occur during receipt and opening of flour containers, mixing, and baking operations.

In larger bakeries, raw materials (flour and sugar) are received in bulk tankers fitted with blowers to discharge material to silos or bins. Silos, which should have a dust collector, are usually used for outside storage; air blowers or in-line sifters are used to transfer the contents to a weighing hopper. Mechanical or pneumatic conveyors are used to move flour from bins; these also require dust collection and explosion vents.

When flour is received by sack or bag, the contents are emptied into bins or used directly from the package. All materials are screened prior to mixing, using a simple sieve or a series of screens. A variety of mixers (examples include horizontal mixers, pressure whisks, and extruders) are used to combine flour and other ingredients. Mixed material must then be divided and shaped prior to cooking; machinery to accomplish this includes rollers, dividers, and depositors. The mixed material then enters the provers, which are heated chambers where yeast fermentation is completed. Finally, products are baked in ovens, after which they may be cooled, sliced or dipped, and wrapped.⁽²⁾

Health Effects of Flour Dust Exposure

Bernardino Ramazzini⁽¹²⁾ reported illness associated with milling and baking as early as 1713, including symptoms of cough, shortness of breath, hoarseness, asthma, and eye problems. The primary work-related illnesses associated with flour exposure continue to be rhinitis, conjunctivitis, Abakers' asthma," and dermatitis. The most serious of these is bakers' asthma.

In a surveillance study of respiratory disease conducted in the United Kingdom from 1989 to 1992, the incidence of bakers= asthma ranged from 290 to 409 per million, making Abaker@ a high risk occupation.^(13,14) In some countries, bakers=asthma is the most common form of occupational asthma. Although modernization and increased automation

have been introduced into the baking and milling industry, bakers=asthma and other associated respiratory allergic disorders continue to be a significant problem among flour-exposed workers, particularly those working in smaller facilities.^(15,17)

Bakers=asthma is characterized by a latency period between the first exposure and the development of symptoms. This latency period can range from a few weeks to 35 years. However, on average, most develop symptoms of allergic rhinitis within 8 to 9 years of exposure and asthma within 13 to 16 years.⁽¹⁸⁾ Symptoms are typically most problematic at work, with improvement noted during weekends or while on vacation.⁽¹⁹⁾ Several studies of occupational asthma imply that most individuals never completely recover from their symptoms, even several years after cessation of exposure.⁽¹⁹⁾ A study of four flour-exposed individuals found that they continued to experience asthmatic symptoms at least 4 years after flour exposure had stopped.⁽²⁰⁾ Once sensitization has occurred, only small quantities of antigen are generally necessary to provoke an asthmatic attack.⁽¹⁹⁾ The asthmatic symptoms can range from mild to persistent and severe.⁽¹⁹⁾ Risk factors contributing to the development of bakers=asthma include length of employment, specific job assignment, and workplace conditions.⁽²¹⁾ Many authors have also noted that a family or personal history of atopy increases the risk of developing bakers=asthma.^(19,21,25) Atopy is defined as the production of antigen-specific antibodies and is most commonly identified by a positive skin reaction to one or more common allergens, such as grass pollens, animal danders, or house dust.⁽²⁶⁾

Although the disease process leading to the development of bakers=asthma is not entirely understood, most evidence indicates that the primary mechanism is a Gell and Coombs Type I immunoglobulin E (IgE) immediate hypersensitivity reaction.^(19,21,27,30) This reaction generally develops shortly after exposure to the antigen, as evidenced by positive skin tests or serum radioimmunoassay tests. Some individuals with bakers=asthma have also demonstrated a dual asthmatic response, with an immediate response occurring initially, followed by a delayed symptom response occurring approximately 3 to 13 hours later. The symptoms associated with the later response are generally longer lasting than those in the immediate phase.^(27,31,32) Symptoms of sneezing, rhinorrhea, and itching eyes usually come before an attack of bakers=asthma.^(33,34)

As indicated in the preceding information, two major contributing factors in the development of

occupational asthma are exposure to the antigen and a history of atopy, both of which play a role in the development of bakers=asthma. A third risk factor for occupational asthma is a history of smoking.⁽²⁶⁾ Surprisingly, this does not appear to be the case with bakers=asthma. One Italian study of 226 bakers and pastry makers found that smoking habits were a predictor of sensitization, with an odds ratio of 2.67.⁽²⁷⁾ However, most other flour-exposure studies that included smoking habits did not find this correlation to sensitization, nor was smoking found to be a factor in the development of other respiratory symptoms.^(16,23,24,35,36)

A report of a fatal case of bakers=asthma was published by Ehrlich in 1994.⁽³⁷⁾ In that case, a 42-year-old male bakery employee with a 5-year history of work-related asthma exhibited daily symptoms of wheezing and dyspnea. His job regularly included pouring flour during mixing operations. After a fourth hospitalization for acute asthma, the individual was given a medication regimen to treat the asthma and reportedly had transferred to a different job within the bakery where he no longer worked directly with flour. However, a year later and shortly after the job transfer, the individual was referred to an occupational diseases clinic during an asthma attack. After positive skin-prick tests to histamine, whole grain wheat, and whole grain maize and a positive response to a flour inhalation challenge test, severe flour hypersensitivity was diagnosed. The individual was advised to leave bakery work but was unable to do so. After new medication and regular visits to the clinic, the individual appeared to be improving 6 months later. One year after the initial clinic visit, however, the individual experienced asthmatic symptoms at work, which continued throughout the weekend at home; he died suddenly the following Monday. Asthma was cited as the cause of death (no autopsy was possible). This case demonstrates the potential danger to those with bakers=asthma with even indirect exposure to flour.

Alderson⁽³⁸⁾ conducted a retrospective study of all males coded as a *Amiller@* or *Abaker@* in the 1991 British census. The cause of death was traced for those individuals who died. The expected number of deaths in the group was estimated, using specific and general age and sex mortality rates. Observed deaths from specific cancers and respiratory conditions were compared to the expected rates. The data indicated there was no significant increase in mortality from respiratory conditions. In addition, there was no evidence of an increase in nasal or lung cancer, although the results were based on small numbers.

Because of its variable composition, different batches of flour can induce different symptoms in sensitive individuals.⁽³⁹⁾ Cereal proteins are likely the most important cause of flour-induced respiratory disorders.⁽²⁶⁾ Approximately 10% of wheat and rye flour is protein.⁽⁴⁰⁾ Through the use of quantitative immunoelectrophoresis methods, investigators were able to identify at least 40 different allergenic protein fractions in wheat extracts.⁽⁴¹⁾ However, the most potent protein allergens were associated with the albumin, globulin, gliadin, and glutenin fractions.⁽⁴²⁾

Several authors have also demonstrated that considerable cross-reactivity exists between the different cereal grains. An early notation of cross-reactivity between wheat, rye, corn, and barley was found in a study of 32 bakers in Massachusetts.⁽⁴³⁾ Other investigators also demonstrated cross-reactivity between wheat and rye in bakers.⁽⁴⁰⁾ By using the radioallergosorbent test (RAST), Baldo et al.⁽²⁸⁾ found that 12 different cereals reacted to sera from individuals sensitized to wheat and rye flour. Wheat, rye, and barley exhibited the highest degree of cross-reactivity and are probably the most common causes of flour hypersensitivity.⁽⁴⁴⁾ The majority of those with symptoms of flour asthma have demonstrated allergy to wheat and rye.⁽³³⁾

Other investigators have also demonstrated cross-reactivity between different cereals by using RAST identification. The taxonomic relationship between the cereals was directly related to the degree of cross-reactivity demonstrated between them. It appears that once an individual is sensitized to one cereal, he or she will be more likely to experience sensitization to one or more of the others.⁽²⁹⁾

Wheat antigens are considered the most allergenic,^(24,34,42) with the water- and salt-soluble fractions containing the most important allergens.^(24,44B46) Significant allergens were also found in the insoluble fractions.⁽⁴²⁾ Flour contains naturally-occurring enzymes such as alpha-amylases, as well as enzyme inhibitors, that can induce flour allergy.^(30,44,47B49)

In addition to the components of the flour dust itself, baking additives and flour contaminants can be causes of bakers' asthma and other respiratory disorders. Baking additives are used to improve the quality of the flour or dough or to quicken the baking process.⁽⁵⁰⁾ Baur et al.⁽⁵⁰⁾ showed that high-molecular-weight enzymes, routinely used in the baking process, sensitized 5% to 24% of a group of symptomatic bakers. Alpha-amylase, in particular, has repeatedly been implicated as the strongest sensitizer added to dough and, although present in smaller amounts than cereal proteins, is a significantly more potent sensitizer.^(5,25,51B54) Alpha-amylase exposure occurs in occupations not

associated with flour, such as the pharmaceutical industry.⁽⁵²⁾ Consequently, exposure to this substance should probably be covered in a separate standard and will not be addressed further in this documentation.

Fisher^(55,56) has noted that benzoyl peroxide, a bleaching agent, and sorbic acid, a preservative, have resulted in the development of allergic dermatitis in bakers. Cereal flours, by the nature of how they are produced and stored, frequently contain contaminants that can also induce bakers' asthma and respiratory allergy. Insects, mites, and molds are the primary allergenic contaminants. Popa et al.⁽⁵⁷⁾ noted that arthropods were a primary contaminant of wheat flour in a study of 43 bakery employees. Eighteen percent had positive skin and bronchial provocation reactions for arthropods. In another study of subjects exposed to wheat and rye flour, Schultze-Werninghaus et al.⁽⁵⁸⁾ found specific IgE to proteins from the flour beetle *Tribolium confusum* in 7.2% of those tested.

Storage mites such as *Lepidoglyphus destructor* (the most common mite associated with flour) have also been studied in relation to their potential to induce asthma and allergy in flour workers. In a study of 43 patients with confirmed sensitization to wheat flour, Armentia et al.⁽⁵⁹⁾ found that 30% also tested positive for *L. destructor*, concluding that flour workers were at increased risk for storage mite allergy. However, other researchers^(25,60,61) have discounted storage mites as a significant allergen among flour workers, showing that there was no increased sensitivity among flour workers as opposed to the general population. These investigators^(25,60,61) concluded that the positive tests were likely due to the widespread presence of storage mites in the general environment.

Finally, Klaustermeyer et al.⁽⁶²⁾ demonstrated hypersensitivity to two molds, *Alternaria* and *Aspergillus*, in two cases of bakers' asthma, concluding that the molds were the causative agents of the asthma.

Animal Studies

Kolopp-Sarda et al.⁽⁶³⁾ have developed a mouse model to study deep-lung immune responses to inhaled flour dust. A total of 15 Swiss male mice (5 in each group) were exposed (nose-only) at 27 " 8 mg/m³ for 3, 6, and, 10 days and sacrificed at the end of the exposure period. A control group contained ten mice. Wheat flour was pulverized in a ring grinder to decrease the particle aerodynamic diameter. A personal Marple impactor was used to characterize the flour dust. Particle size was found

to range from 0.1 to 10 μm (data were not reported as a histogram or size distribution). All animals were sacrificed on the day 11 of the experiment. Direct immunofluorescence was used to analyze the T, B, and plasma cells, while enzymatic reaction was used to evaluate macrophage.

Acute exposure to flour resulted in rapid immune modifications of the deep lung. These modifications were quickly controlled. Transient inflammatory reactions were evident, based upon elevated macrophage levels, but there was an absence of notable inflammatory sites in the lung tissue. A longer-lasting effect noted was a decrease in the number of B cells. The authors⁽⁶³⁾ concluded this could be due to repeated immune responses from prolonged exposure to flour antigens and, therefore, could be a specific step in the development of tolerance.

Human Studies/Reports

There have been many studies of the allergic and immunologic characteristics of flour dust since the 1930s. Only those studies which describe exposure levels or health effects in relevant populations are discussed in this section.

Herxheimer^(64,65) conducted a large 5-year cohort study in Germany of bakers=apprentices newly entering the trade. In the first year, 880 apprentices were enrolled into the study and tested annually for skin reactions to wheat flour, rye flour, and other allergens. Of note, 8% showed a positive reaction to wheat flour within 1 month of the start of their apprenticeships. Although some of the apprentices who tested positive during the first year were negative in subsequent years, the percent of those testing positive continued to increase from 8% in year 1 to 12% in year 2, 19% in year 3, 27% in year 4, and 30% after 5 years. Not all of those testing positive experienced clinical illness. Unfortunately, the study experienced a huge loss to follow-up (approximately 50% after the third year and over 90% by the fifth year), leaving some of the results open to question. This study did not describe flour dust exposures for these workers.

Thiel and Ulmer⁽³⁴⁾ studied 152 flour-exposed workers in Germany and found that the intensity of respiratory illness increased as duration of employment increased. Only 1 of 85 (1%) baker's apprentices was diagnosed with bakers' asthma in the third year of apprenticeship, while the disease was diagnosed for 3 of 29 (10%) apparently healthy bakers (mean occupation time of 25 " 6 years) and for 31 of 38 (82%) bakers with "proven" occupational

disease (mean employment time of 25 " 8 years). Dust exposures were not reported in this study.

Prichard et al.⁽²³⁾ studied respiratory symptoms and function among 200 men with more than 5 years of employment from 18 metropolitan bakeries in Perth, Australia; 176 bakers and 24 employees responsible for slicing and wrapping bread were included, representing 90% of all bakers in this area. Most of the bakers (68%) worked in three large automated bakeries as managers, ingredient preparers, dough makers, oven handlers, and slicers/wrappers. The remainder of the subjects were from 15 smaller bakeries where tasks were less automated and specialized. These were classified as general bakers because they were involved in all baking tasks.

Of the 176 bakers, 20 demonstrated work-related asthma. When compared to the remaining 156 bakers, these 20 showed significantly higher prevalences of chronic bronchitis, increased bronchial reactivity, and positive skin-prick tests. Smoking history and age were similar for the two groups. There was no difference in height- and age-standardized forced expiratory volume at 1 second (FEV₁) between these two groups.

Comparisons among the three occupational groups thought to have the highest flour dust exposure (16 oven handlers, 29 general bakers, and 17 dough makers) showed a greater prevalence of wheeze and breathlessness in the oven handlers (44%) than in the general bakers (14%) or dough makers (24%). Average standardized FEV₁ was significantly less among the oven handlers (3.54 L) than among either the general bakers (4.05 L) or dough makers (4.12 L).

Hartmann et al.⁽⁶⁶⁾ studied 314 bakery workers and found a prevalence of 74% for respiratory allergy, either as rhinitis or asthma.

In the Sudan, Awad el Karim et al.⁽⁶⁷⁾ evaluated the prevalence of respiratory and allergenic disorders in 100 male workers exposed to grain and flour dusts. Thirty male controls who did not work with flour were also evaluated. Total and respirable dust concentrations were measured in various sections throughout the mill. However, it was not specified in the study whether the samples were personal or stationary, nor was the sampler described. Mean concentrations of total dust ranged from 1.4 to 3.6 mg/m³, while the mean respirable dust concentrations ranged from 0.3 to 0.8 mg/m³. The lowest mean concentrations (both total and respirable) were measured in the wheat store, and the highest were found among the plant sifters.

An analysis of respiratory symptoms showed that the mill workers had a significantly increased

prevalence of chronic cough, phlegm, chronic bronchitis, chest tightness, bronchial asthma, chronic rhinitis, urticaria, sinusitis, and conjunctivitis, when compared to the controls. The number of positive skin reactions to wheat flour extract was also significantly greater for the millers compared with the controls. Lung function tests revealed a drop in FEV₁ and forced vital capacity (FVC) in 58% of the exposed workers after the end of their shifts. The ventilatory capacity of the exposed group fell significantly at the end of the work shift, while that of the controls did not.

Musk et al.⁽¹⁶⁾ undertook a cross-sectional study of 279 employees in a large British bakery to assess dust exposure, estimate the prevalence of symptoms and sensitization among the workers, and describe the exposure-response relationship. Employment categories were ranked from 0 to 10 by "perceived dustiness." Open-face Casella filter holders with 25-mm glass microfiber filters or closed-face Millipore 37-mm cassettes with polycarbonate membrane filters were used to take 79 personal samples from various areas throughout the bakery. The samples were analyzed gravimetrically for total dust. The geometric mean (GM) of the exposures among the ten employment categories ranged from 0.01 to 11 mg/m³. The two highest exposed employment categories were those preparing ingredients in the confectionary bakery (GM = 11 mg/m³) and the flour room/scone production staff (GM = 6.6 mg/m³). Eighteen samples exceeded 10 mg/m³ in the ingredients preparation and manufacturing areas. In general, the dust measurements agreed with the ranking of employment categories for levels of perceived dustiness. Geometric mean dust levels were generally greater than 2 mg/m³ for all exposure categories of rank 6 and higher. Ingredients preparation and a pastry flour room had much higher mean concentrations (11 and 6.6 mg/m³, respectively).

Study participants completed a self-administered questionnaire on respiratory symptoms and were evaluated for pulmonary function and nonspecific bronchial reactivity. In addition, skin tests for multiple environmental and flour allergens were performed. For 234 of the workers (excluding all of those in exposure rank 5 who performed maintenance activities and some in rank 7 who worked only intermittently), 13% reported chronic bronchitis, and 19% reported dyspnea and work-related nasal symptoms.

When workers in the "main" group (234) were divided into exposure ranks, the percent reporting symptoms were generally higher for those with exposure ranks of 6 or greater. Chronic bronchitis

was almost 4 times as prevalent in the higher exposure group, and work-related wheeze and nasal symptoms were twice as prevalent.

Workers in the higher exposure group were approximately 1.5 times more likely to have standardized values of FEV₁/FVC < 70%. The prevalence of positive skin tests for bakery antigens was also 1.5 times greater in the more highly exposed workers.

Tee et al.⁽⁶¹⁾ analyzed 55 of the 79 personal flour dust samples obtained in the study by Musk et al.⁽¹⁶⁾ (described above) for flour allergen content, using RAST inhibition. In general, flour aeroallergen levels increased with increasing job exposure rank. When total dust concentrations were compared with flour allergen levels, the relationship was a linearly increasing one above dust levels of 5 mg/m³. For dust levels below 5 mg/m³, no clear relationship was found; in general, flour allergen levels were very low in these samples.

Total dust levels in 6 Finnish bakeries with 10 to 30 production workers were evaluated by another group of investigators.⁽⁵⁾ The 27 personal samples, using membrane filters in open-face, three-piece cassettes at 2 to 2.5 L/min, were taken during weighing of flour and flour additives, dough making, and bread making. Most samples were for 4 to 7 hours; sampling time for weighing flour additives ranged from 10 to 40 minutes. Dust levels were determined gravimetrically; samples were then analyzed for alpha-amylase using a colorimetric enzymatic method.

Weighing and dough making were on average dustier (mean, 4.2 and 4.6 mg/m³, respectively) than bread making (mean of 2.3 mg/m³). Alpha-amylase levels were considerably higher during flour and additive weighing than during any other task. The prevalence of respiratory symptoms in these workers was not addressed in this study.

In Finland, Masalin et al.⁽⁶⁸⁾ conducted a study to determine levels of exposure to flour and sugar dusts in a large confectionery factory. Forty-nine personal samples were taken from the breathing zone of the factory workers. PVC filters were used, but the type of sampler was not specified. The samples were first analyzed for dust by gravimetric methods. Each sample was then halved and analyzed separately for wheat flour and sucrose content. The amount of wheat flour was determined for 43 samples by analyzing for linoleic acid, a fatty acid component of wheat fat. High-pressure liquid chromatography was used to analyze the sucrose content of 42 samples. The sum of the sucrose and flour dust analyses exceed the dust amounts in some instances, possibly due to nonuniformity of the filter halves and inconsistent linoleic acid content. Dust levels ranged from 0.1 to 47.7 mg/m³.

The measured concentration range for the wheat flour portion of the samples was 0.01 to 8.1 mg/m³ (GM = of 1.7 mg/m³). The highest dust concentrations were measured during the preparation of cake mixes.

De Zotti et al.⁽²⁵⁾ conducted a survey of 226 employees from 105 Italian bakeries and pastry shops. Skin-prick tests for common allergens, storage mites, flour, and other allergens were done. Results of the skin tests showed 12% positive for wheat flour and 7.5% positive for alpha-amylase. Atopy was demonstrated by 24% of the group. Half of the participants reported work related asthma, 18% rhinoconjunctivitis, and 10% chronic bronchitis. Only flour-exposed workers demonstrated sensitization to wheat flour, when compared with 119 white-collar office workers. Skin tests for other flours were not as specific.

Burdorf et al.⁽⁴⁾ conducted a study in Sweden to characterize exposure to inhalable flour dust in bakeries. (Alpha-amylase and protein analyses were also carried out but are not discussed here.) Employees from 12 bakeries were assigned to exposure groups based upon principle job task. Personal air sampling was conducted with IOM inhalable samplers with cellulose acetate filters. The samples were analyzed gravimetrically. The size distribution of the airborne flour dust was also measured using IOM personal, inhalable, aerosol spectrometers. Sampling times ranged from 42 to 435 minutes.

Workers were assigned to one of six exposure groups: dough makers, bread formers, confectionery workers, oven workers, packers, and mixed tasks. The GM of all inhalable dust measurements was 2.5 mg/m³ (range 0.1B17 mg/m³), while the arithmetic mean (AM) was 3.8 mg/m³. Dough makers had the highest flour dust exposures (GM = 5.5 mg/m³), followed by the bread formers (GM = 2.7 mg/m³), those with mixed tasks (GM = 2.7 mg/m³), and oven workers (GM = 1.2 mg/m³). Packers and confectionery workers had the lowest exposures (GM = 0.5 and 0.6 mg/m³, respectively).

The results from the size distribution measurements indicated that approximately 40% of the dust was in the thoracic fraction, and 19% was in the respirable fraction. The aerosol appeared to be bimodal, with one mode at a particle size less than 1 µm and the second at about 12 µm.

Nieuwenhuijsen et al.⁽¹⁰⁾ measured personal exposures to total dust and flour aeroallergen in three flour mills (60B200 employees), one flour packing station (30 employees), and three large modern bakeries (200B450 employees) in Britain.

This survey was part of a 7-year prospective longitudinal study designed to look at the relationship between flour exposure and the development of symptoms, as well as the relationship between flour exposure and the development of sensitization. Employees were divided into exposure groups based upon work tasks and job titles. A total of 495 entire-shift personal samples were collected from randomly selected workers within each exposure group. Seven-hole samplers containing polytetrafluoroethylene filters were used. Total dust concentrations were determined by weight, and samples were then analyzed for aeroallergen concentration, using a rabbit antibody-based competitive inhibition assay.

The geometric mean of the total dust concentrations ranged from 0.4 to 6.4 mg/m³ in the bakeries and from 0.5 to 17 mg/m³ in the flour mills and packing station. The GM of airborne flour allergen levels ranged from 46 to 252 µg/m³ in the bakeries and from 102 to 1728 µg/m³ in the flour mills and packing stations. The highest dust exposures occurred in the flour packing areas, dough brakes, and mixing areas.

In general, the pattern of flour aeroallergen concentrations was similar to that of the total dust concentrations. Strong linear relations between the measurements were noted in the mixing areas, but not in areas where nonflour products made up a portion of the total dust concentration. The authors⁽¹⁰⁾ concluded that total dust measurements are approximations which may accurately reflect flour exposure when the dust is consistently flour but could lead to overestimation in areas where high amounts of nonflour products are present.

As a companion survey to the Nieuwenhuijsen et al.⁽¹⁰⁾ study described above, Cullinan et al.⁽³⁶⁾ conducted a cross-sectional survey during the 7-year cohort study. The purpose was to correlate exposure with new incidence of work-related symptoms. Consequently, those workers with previous flour exposure were excluded. Questionnaires were completed for 264 participants. The frequency of new work-related symptoms generally increased with exposure intensity, particularly for eye and nose symptoms.

Lillienberg and Brisman⁽¹⁷⁾ conducted a series of flour dust measurements in bakeries and flour-mixing factories in order to compare two different samplers. Side-by-side IOM inhalable samplers and 37-mm cassettes were used to obtain 29 personal samples of flour dust. In addition, aerosol particle-size distribution was determined using a personal inhalable dust spectrometer.

The mean dust concentration for the IOM inhalable sampler ranged from 1.0 to 20 mg/m³ and from 0.6 to 8.5 mg/m³ for the 37-mm cassette. A linear correlation was demonstrated between the two sets of sampling data, with the IOM sampler collecting approximately two times the amount of dust as the 37-mm cassette. (Only the filter from the IOM was evaluated; some undersampling may have occurred as a result.) The mean exposure measurements for the flour-mixing factories were much higher than those of the bakeries. The dough-making and bread-forming (in-line) production areas had the highest exposures in the bakeries.

The aerosol size distribution was found to be bimodal, with the smallest particles having an aerodynamic diameter of approximately 5 µm and the larger particles having an aerodynamic diameter of approximately 20 µm. The aerosol in the mixing areas was generally larger, with the first mode at 9 µm and the second at 25 µm. The aerosol in the oven area was generally much smaller, with only one mode at about 1 µm.

Kolopp-Sarda et al.⁽⁶³⁾ sampled dust levels for 60 male workers in 11 flour mills and 1 industrial bakery in France. Personal samples were taken over 2 consecutive days. The sampler was not specified. The mean dust concentration from the mill samples was 10 mg/m³ (standard deviation [SD] = 13 mg/m³). Concentrations as high as 45 mg/m³ were found in the packaging areas. The mean dust concentration from the bakery samples was 4.9 mg/m³ (SD = 9.1 mg/m³). Bakers were the most exposed, while oven workers had the lowest levels.

Sandiford et al.⁽⁶⁹⁾ used a personal eight-stage cascade impactor (Sierra Marple) to determine the particle size distribution of flour dust in a flour mill and bakery. Fifteen samples (5 at each of 3 sites) were taken. The data presented in this paper suggest that the mass median aerodynamic diameter was about 45 µm for the bakery roll production area, > 20 µm in the bakery dough-brake area, and between 15 and 20 µm in the flour mill packing area.

Bohadana et al.⁽³⁵⁾ measured flour dust exposure levels in an industrial bakery in France. These measurements were part of a cross-sectional survey to determine the relationship between respiratory symptoms, sensitization to wheat flour antigens, and airway responsiveness. Forty-four flour-exposed employees and 164 nonflour-exposed controls from other manufacturing industries were studied. Total dust concentrations were determined by personal air sampling using closed-face 37-mm cassettes with glass microfiber filters. A total of 21 samples were collected from 5 different areas.

The mean concentrations ranged from 0.69 to 41.3 mg/m³. The mean dust levels were < 10 mg/m³ with the exception of one area where special baking practices were employed (mean of 41.3 mg/m³). The proportion of workers reporting one or more respiratory symptoms was greater than that of the controls. Symptoms were not significantly related to dust exposure. Workers exposed to flour had significantly lower baseline pulmonary function tests than controls. Flour-exposed workers had a significantly greater number of positive airway responsiveness tests than controls. The authors concluded that workers showed a significantly greater number of respiratory symptoms and airway responsiveness abnormalities than the controls did at exposure levels generally less than 10 mg/m³.

Peak exposure levels to total dust and flour aeroallergen at three large bakeries and one flour mill packing station were evaluated by investigators in the United Kingdom.⁽¹¹⁾ Employees were divided into exposure groups based upon job tasks. Seven-hole samplers were used to collect 209 personal samples over the duration of the task (2 minutes to 4 hours) and analyzed for total dust and flour aeroallergen.

The GM for flour dust ranged from 1.4 to 97 mg/m³. The GM for flour aeroallergen ranged from 18.6 to 3808 µg/m³. In general, average flour aeroallergen dust levels increased linearly with average flour dust concentrations. Cleaners and operators had the highest concentrations of flour dust and flour aeroallergen. The task samples generally showed higher measured concentrations than full-shift samples (measured during a previous study).

Massin et al.⁽⁷⁰⁾ measured dust exposures and respiratory health for 118 male employees in 11 mills in eastern France. Controls (164) were drawn from workers at six manufacturing plants in the same geographic region with no flour exposure. Personal dust samples were taken for 5 to 7 hours over 2 days, using closed-face 37-mm cassettes with 4-mm diameter openings, operated at 1 L/min (claimed to match the ISO and CEN inhalable sampling criteria). Respiratory health was assessed by medical history, pulmonary function tests, and airway responsiveness using a methacholine challenge. Skin-prick tests were also performed using a wheat flour extract.

Dust concentrations ranged from 1 to 79 mg/m³, with a great deal of variability within worker categories. Sacking workers and those with a mixture of tasks had the highest mean exposures (14.3 and 13.8 mg/m³, respectively). Prevalence of cough and chronic bronchitis was significantly greater in the flour-exposed workers when compared with controls. Both groups had similar

prevalences of asthma and nasal symptoms. Positive skin tests were found in 7% of the mill workers and in none of the controls. Baseline FEV₁ was similar among the two groups. Positive airway responsiveness tests were more prevalent in the flour-exposed group than in the controls. The authors⁽⁷⁰⁾ did not attempt to relate different exposure levels to respiratory symptoms. Neither current nor cumulative exposure appeared to be related to any of the health effect outcomes.

Shamssain⁽⁷¹⁾ studied respiratory symptoms and ventilatory capacity in 63 male flour-processing workers in South Africa. Controls were employees of a bottling plant. Flour-exposed workers had a significantly higher prevalence of respiratory symptoms than the controls and significantly lower forced expiratory indices than the controls.

Gimenez et al.⁽⁷²⁾ evaluated chronic and acute respiratory effects among mill workers exposed to flour. One hundred forty-two mill workers and 37 controls were evaluated using standardized questionnaires and pulmonary function tests. Airborne dust exposures were measured by personal sampling, using 37-mm cassettes with glass fiber filters. Sampling for the respirable fraction of the dust was accomplished with the use of cyclones. Dust concentrations for seven samples ranged from 5.43 to 53.9 mg/m³. The respirable concentrations of four samples ranged from 0.16 to 0.35 mg/m³. Interpretation of the sampling results is limited because of the small sample size. The prevalence of respiratory symptoms was higher in the flour-exposed workers than in the controls. Lower pulmonary function test values were noted in workers than in controls.

Houba et al.⁽⁷³⁾ collected 546 personal, inhalable dust samples using PAS-6 samplers and Teflon⁷ filters. The samples were analyzed gravimetrically; 449 were then further analyzed for wheat flour antigens using enzyme-linked immunosorbent assay (ELISA) inhibition. Twenty-one bakeries were included in the study; the 5 largest had 10 to 200 employees, while the remaining 16 smaller bakeries had 1 to 6 employees. Employees were grouped into nine exposure categories according to job title. The personal dust exposure GM for all job categories was 1.0 mg/m³, with a range of 0.1 to 37.1 mg/m³. Average dust exposures in the larger bakeries were lowest for slicers, packers, and transport workers (GM = 0.4 mg/m³) and highest for dough makers (GM = 3.0 mg/m³). All job categories, with the exception of dough makers, had GM exposures less than 1 mg/m³. In the smaller bakeries, the GM dust exposures were 0.7 mg/m³ for confectioners,

2.0 mg/m³ for mixed bakers, and 3.3 mg/m³ for bread bakers.

The personal wheat antigen exposure GM for all job categories was 684 ng/m³, with a range of 33 to 252,407 ng/m³. The trend of measured results among the exposure groups was similar for the inhalable dust and wheat antigen measurements. Dough makers in large bakeries and bread bakers in small bakeries had the highest levels (GM = 5323 and 5989 ng/m³, respectively).

The relationships in exposures between different job categories were not consistent for dust and wheat antigens. For example, dough makers had 7.5 times greater dust exposures than slicers and packers, but 69 times higher wheat antigen levels. The antigen-to-dust ratio was not consistent across job categories. Greater differences in these ratios were found in larger bakeries than in the small ones.

Among all dough makers, exposure to wheat flour varied, depending on the product. Dough makers at wheat bread production sites had the highest wheat antigen exposures.

The authors⁽⁷³⁾ argue that measuring wheat antigen levels offers two advantages over assessing dust levels. First, wheat antigen levels represent more closely the etiologic agent thought to be responsible for the majority of bakers=asthma and other flour dust-related health effects. Second, they are a more sensitive measure of exposure than dust and allow better detection of exposure differences among different categories of workers. In production areas where wheat flour is only one of many ingredients, dust levels are confounded and unrepresentative of flour dust exposures.

Burstyn et al.⁽⁷⁴⁾ measured 8-hour personal exposures to dust using seven-hole samplers for 96 workers in 7 bakeries while observing 14 tasks at 15-minute intervals. Dust levels ranged from 0.1 to 110 mg/m³ (mean of 8.3 mg/m³); weighing, pouring, operating dough brakes and sheeters were associated with the highest levels of dust. The use of divider oil was associated with very low levels (GM = 0.2 mg/m³), and automated dough-forming created lower dust levels than manual operations.

Zuskin et al.⁽⁷⁵⁾ studied 53 flour packers in Croatia and compared respiratory symptoms with 65 unexposed workers in the same confectionary industry. Significantly higher prevalences of chronic respiratory symptoms, including cough, phlegm, bronchitis, dyspnea, nasal catarrh, and sinusitis, were found in the exposed group. Prevalence of acute symptoms during the work shift was also high, especially for cough (57%) and eye irritation (55%). Positive skin tests to flour were significantly

higher in prevalence among the flour-exposed workers (36%) than among the controls (10%).

Dust levels were measured in the work areas using a two-stage Hexhlet sampler. Total dust concentrations ranged from 2.4 to 17.1 mg/m³ (mean = 12.3 mg/m³); respirable levels ranged from 0.5 to 2.7 mg/m³ (mean = 1.9 mg/m³).

A cross-sectional study by Houba et al.⁽⁷⁶⁾ of 393 workers in 21 bakeries showed a strong positive relationship between wheat flour allergen exposure and wheat flour sensitization. Exposures were measured using personal inhalable samplers (PAS-6); wheat flour was recovered from the filters and wheat allergen concentrations were measured by inhibition enzyme immunoassay. Venous blood samples were analyzed for total IgE and specific IgE antibodies; atopy was defined on the basis of these data. All workers completed a self-administered respiratory-symptoms questionnaire. Three exposure groups were formed using job titles; the GM inhalable dust levels for the low, medium, and high exposure groups were 0.5, 0.8, and 2.4 mg/m³, respectively. The predominant job title in the highest exposure group was Adough makers.®

Increasing likelihood of wheat-specific IgE sensitization was associated increasing wheat allergen exposure. This doseBresponse relationship was steepest for atopic workers. Atopics with high wheat allergen exposure were 5.2 (confidence interval [CI] 1.6B16.2) times more likely to be sensitized when compared with workers in the low exposure group; atopics in the medium exposure group were 2.7 (CI 0.5B14.5) times more likely to be sensitized. Nonatopics in the high and medium exposure groups were 2.5 (CI 0.8B7.5) and 1.4 (CI 0.3B64.) times more likely to be sensitized than those at the low exposure. The prevalence of symptoms also increased with increasing wheat allergen exposure; the strongest relationship was found for sensitized workers.

The authors⁽⁷⁶⁾ suggest that exposures should be reduced to the lowest exposure category (0.2 ìg/m³ wheat allergen or approximately 0.5 mg/m³ inhalable dust) to minimize the rate of sensitization and the likelihood of symptoms in those already sensitized.

Sampling Airborne Flour Dust

It appears that flour dust consists of particles ranging from as small as 1 ìm to greater than 20 ìm in size. Depending on the location and task, aerosols may contain one or more modes centered somewhere near 1 to 5 ìm and 15 to 30 ìm.

Flour dust appears to cause symptoms throughout the respiratory tract, ranging from rhinitis

in the nasal area to chronic bronchitis and asthma in the lungs. These symptoms correlate well with the aerosol size distributions described above. It is clear that an inhalable guideline is most appropriate to account for all health effects.

Only one side-by-side study of "total" and inhalable samplers has been carried out to date.⁽¹⁷⁾ The results suggest that inhalable samplers will generally measure twice that of "total" samplers, although this may be an underestimate of the true relationship between these two types of samplers because the study evaluated only the filter and not the entire cassette from the IOM inhalable sampler.

A large number of studies of respiratory symptoms, skin sensitization, and lung function have been carried out in a variety of countries. Few of these, however, have measured dust levels. Where exposures have been measured, not enough information about the relationship between dust levels and health effects is available to establish a clear doseBresponse relationship. On the other hand, many studies of dust exposure are available but provide few or no data about respiratory or other health effects.

TLV Recommendation

Awad el Karim et al.⁽⁶⁷⁾ found changes in lung function tests and an increased prevalence of respiratory and asthmatic symptoms with exposure to total flour dust levels of 1.35 to 3.57 mg/m³. Masalin et al.⁽⁶⁸⁾ demonstrated that the range of measured total dust levels can be large (0.1B48 mg/m³). Musk et al.⁽¹⁶⁾ found an increase in the prevalence of chronic bronchitis, work-related wheeze, and work-related nasal symptoms for workers with total flour dust exposures greater than approximately 2 mg/m³. Cullinan et al.⁽³⁶⁾ found an increase in work-related respiratory symptoms for workers with total dust exposures greater than 5 mg/m³. Bohadana et al.⁽³⁵⁾ found that mean dust levels in an industrial bakery were < 10 mg/m³, with the exception of one area. Workers in that study reported more respiratory symptoms than the controls, had a significantly greater number of positive airway responsiveness tests than the controls, and had significantly lower baseline pulmonary function tests than the controls. Gimenez et al.⁽⁷²⁾ noted an increased prevalence of respiratory symptoms among exposed workers than controls for total flour dust concentrations of 5.4 to 54 mg/m³. The findings of Houba et al.⁽⁷³⁾ indicate that wheat flour sensitization may occur at dust levels as low as 0.5 mg/m³ inhalable dust (or 0.2 ìg/m³ wheat allergen).

In many of the studies noted above, flour dust was classified as a particulate not otherwise classified (PNOC), and the exposure limit expressed as 10 mg/m³. However, flour dust has been demonstrated to be a complex mixture of many components capable of inducing sensitization and respiratory symptoms at much lower levels. The literature suggests that a level well below 10 mg/m³ total dust is necessary for preventing sensitization by flour dust exposure. The work by Houba et al.⁽⁷⁶⁾ supports a level of 0.5 mg/m³ inhalable dust as one that will prevent or at least minimize the prevalence of wheat flour sensitization. Therefore, ACGIH recommends a TLV-TWA of 0.5 mg/m³ for occupational exposure to inhalable flour dust to protect against sensitization and other respiratory symptoms. The SEN notation is justified by data from numerous studies cited and discussed in this Documentation.

Other Occupational Exposure Values

There are no recommendations from other agencies or countries specific to flour dust. Some countries have recommendations for organic dusts: Croatia: 3 mg/m³ total dust, 1 mg/m³ respirable dust; Denmark: 3 mg/m³ total dust; Finland, Iceland, Norway, Sweden: 5 mg/m³ total dust.

References

1. Cesaro, A.N.; Granata, A.: Flour Milling. In: Encyclopaedia of Occupational Health and Safety, 3rd ed., Vol. 1. L. Parmeggiani, Ed. International Labour Organization, Geneva (1983).
2. Street, C.A.: Flour Confectionary Manufacture. VCH Publishers, New York (1991).
3. Pillsbury Flour Mills Company: Pillsbury. The Story of Flour. Pillsbury Flour Mills Co., Minneapolis, MN (1925).
4. Burdorf, A.; Lillienberg, L.; Brisman, J.: Characterization of Exposure to Inhalable Flour Dust in Swedish Bakeries. *Ann. Occup. Hyg.* 38(1):67B78 (1994).
5. Jauhiainen, A.; Louhelainen, K.; Kinnainmaa, M.: Exposure to Dust and alpha-Amylase in Bakeries. *Appl. Occup. Environ. Hyg.* 8(8):721B725 (1993).
6. Harwood, J.L.; Leath, M.N.; Walter, G.; Heid, J.: The U.S. Milling and Baking Industries. Report No. 611. U.S. Department of Agriculture, Washington, DC (1989).
7. Board WAO. Wheat Outlook. Online at: http://mann77.mannlib.cornell.edu/reports/erssor/field/whs-bb/1997/wheat_outlook_01.13.97. Economic Research Service, U.S. Department of Agriculture, Washington, DC (1997).
8. Valdivieso, R.; Pola, J.; Zapata, C.: Farm Animal Feeders: Another Group Affected by Cereal Flour Asthma. *Allergy* 43:406B410 (1988).
9. Villard, R.F.: Encyclopaedia of Occupational Safety and Health, 3rd ed., Vol. 1. L. Parmeggiani, Ed. International Labour Organization, Geneva (1983).
10. Nieuwenhuijsen, M.J.; Sandiford, C.P.; Lowson, D.; et al.: Dust and Flour Aeroallergen Exposure in Flour Mills and Bakeries. *Occup. Environ. Med.* 51:584B588 (1994).
11. Nieuwenhuijsen, M.J.; Sandiford, C.P.; Lowson, D.; et al.: Peak Exposure Concentrations of Dust and Flour Aeroallergen in Flour Mills and Bakeries. *Ann. Occup. Hyg.* 39(2):193B201 (1995).
12. Ramazzini, B.: Diseases of Workers. The University of Chicago Press, Chicago (1940).
13. Meredith, S.K.; Taylor, V.M.; McDonald, J.C.: Occupational Respiratory Disease in the United Kingdom 1989: A Report to the British Thoracic Society and the Society of Occupational Medicine by the SWORD Project Group. *Br. J. Ind. Med.* 48:292B298 (1991).
14. Meredith, S.K.; McDonald, J.C.: Work-Related Respiratory Disease in the United Kingdom, 1989B1992: Report on the SWORD Project. *Occup. Med.* 44:183B189 (1994).
15. VanDishoeck, H.A.E.; Roux, D.J.: Sensitization to Flour and Flour Illnesses Amongst Flour Workers. *J. Hyg.* 39:674B679 (1939).
16. Musk, A.W.; Venables, K.M.; Crook, B.; et al.: Respiratory Symptoms, Lung Function, and Sensitization to Flour in a British Bakery. *Br. J. Ind. Med.* 46:636B642 (1989).
17. Lillienberg, L.; Brisman, J.: Flour Dust in Bakeries C A Comparison Between Methods. *Ann. Occup. Hyg.* 38(Suppl. 1):571B575 (1994).
18. Slankard-Chahinian, M.: Bakers' Asthma. In: Occupational Asthma. C.A. Frazier, Ed. Van Nostrand Reinhold, New York (1980).
19. Chan-Yeung, M.: Occupational Asthma. *Chest* 98(5):148sB161s (1990).
20. Allard, C.; Cartier, A.; Ghezzi, H.; Malo, J.-L.: Occupational Asthma Due to Various Agents: Absence of Clinical and Functional Improvement at an Interval of Four or More Years after Cessation of Exposure. *Chest* 96(5):1046B1048 (1989).
21. Zeitz, H.: Bakers' Asthma. *Allergy Proc.* 11(2):63B64 (1990).
22. Jarvinen, K.A.J.; Pirila, V.; Bjorksten, F.; et al.: Unsuitability of Bakery Work for a Person with Atopy: A Study of 234 Bakery Workers. *Ann. Allergy* 42(3):192B195 (1979).
23. Prichard, M.G.; Ryan, G.; Musk, A.W.: Wheat Flour Sensitization and Airways Disease in Urban Bakers.

- Br. J. Ind. Med. 41:450B454 (1984).
24. Prichard, M.G.; Ryan, M.G.; Walsh, B.J.; Musk, A.W.: Skin Test and RAST Responses to Wheat and Common Allergens and Respiratory Disease in Bakers. Clin. Allergy 15:203B210 (1985).
 25. De Zotti, R.; Larese, F.; Bovenzi, M.; et al.: Allergic Airway Disease in Italian Bakers and Pastry Makers. Occup. Environ. Med. 51:548B552 (1994).
 26. Taylor, A.J.N.: Occupational Asthma. In: Occupational Lung Disorders, 3rd ed. W.R. Parks, Ed. Butterworths-Heinemann, London (1994):
 27. Wilbur, R.D.; Ward, G.W.: Immunologic Studies in a Case of Baker's Asthma. J. Allergy Clin. Immunol. 58(3):366B372 (1976).
 28. Baldo, B.A.; Krilis, S.; Wrigley, C.W.: Hypersensitivity to Inhaled Flour Allergens. Allergy 35:45B56 (1980).
 29. Block, G.; Tse, K.S.; Kijek, K.; Chan-Yeung, M.: Bakers' Asthma: Studies of the Cross-Antigenicity Between Different Cereal Grains. Clin. Allergy 14:179B185 (1984).
 30. Franken, J.; Staphan, U.; Meyer, H.E.; Konig, W.: Identification of alpha-Amylase Inhibitor as a Major Allergen of Wheat Flour. Int. Arch. Allergy Immunol. 104:171B174 (1994).
 31. Nakazawa, T.; Tohoda, T.; Furukawa, M.; et al.: Inhibitory Effects of Various Drugs on Dual Asthmatic Responses in Wheat Flour-Sensitive Subjects. J. Allergy Clin. Immunol. 58(1):1B9 (1976).
 32. Hendrick, D.J.; Davies, R.J.; Pepys, J.: Bakers' Asthma. Clin. Allergy 6:241B250 (1976).
 33. Chan-Yeung, M.; Malo, J.-L.: Aetiological Agents in Occupational Asthma. Eur. Respir. J. 7:346B371 (1994).
 34. Thiel, H.; Ulmer, W.T.: Bakers' Asthma: Development and Possibility for Treatment. Chest 78(2 Suppl.):400B405 (1980).
 35. Bohadana, A.B.; Massin, N.; Wild, P.; et al.: Respiratory Symptoms and Airway Responsiveness in Apparently Healthy Workers Exposed to Flour Dusts. Eur. Respir. J. 7:1070B1076 (1994).
 36. Cullinan, P.; Lowson, D.; Nieuwenhuijsen, M.J.; et al.: Work-Related Symptoms, Sensitisation, and Estimated Exposure in Workers Not Previously Exposed to Flour. Occup. Environ. Med. 51:579B583 (1994).
 37. Ehrlich, R.I.: Fatal Asthma in a Baker: A Case Report. Am. J. Ind. Med. 26:799B801 (1994).
 38. Alderson, M.R.: Mortality of Millers and Bakers. Br. J. Cancer 55:695B696 (1987).
 39. Napolitano, J.; Weiss, N.S.: Occupational Asthma of Bakers. Ann. Allergy 40:258B261 (1978).
 40. Bjorksten, F.; Backman, A.; Jarvinen, K.A.J.; et al.: Immunoglobulin E Specific to Wheat and Rye Flour Proteins. Clin. Allergy 7:473B483 (1977).
 41. Blands, J.; Diamant, B.; Kallos-Deffner, L.; Lowenstein, H.: Flour Allergy in Bakers: Identification of Allergenic Fractions in Flour and Comparison of Diagnostic Methods. Int. Arch. Allergy Appl. Immunol. 52:392B406 (1976).
 42. Walsh, B.J.; Wrigley, C.W.; Musk, W.W.; Baldo, B.A.: A Comparison of the Binding of IgE in the Sera of Patients with Bakers' Asthma to Soluble and Insoluble Wheat-Grain Proteins. J. Allergy Clin. Immunol. 76:23B28 (1985).
 43. Comes, A.; Guild, B.T.; Rackemann, R.M.: Studies in Sensitization: Influence of Occupation on Sensitization in Man as Determined in a Study of Thirty-Two Bakers. J. Allergy 6:539B547 (1935).
 44. Sandiford, C.P.; Tee, R.D.; Taylor, A.J.N.: Identification of Cross-Reacting Wheat, Rye, Barley and Soya Flour Allergens Using Sera from Individuals with Wheat-induced Asthma. Clin. Exp. Allergy 25:340B349 (1995).
 45. Pfeil, T.; Schwabl, U.; Ulmer, W.T.; Konig, W.: Western Blot Analysis of Water-Soluble Wheat Flour (*Triticum vulgaris*). Int. Arch. Allergy Appl. Immunol. 91:224B231 (1990).
 46. Sutton, R.; Skeritt, J.H.; Baldo, B.A.; Wrigley, C.W.: The Diversity of Allergens Involved in Bakers' Asthma. Clin. Allergy 14:93B107 (1984).
 47. Sandiford, C.P.; Tee, R.D.; Taylor, A.J.N.: The Role of Cereal and Fungal Amylases in Cereal Flour Hypersensitivity. Clin. Exp. Allergy 24:549B557 (1994).
 48. Barber, D.; Sanchez-Monge, R.; Gomez, L.; et al.: A Barley-Four Inhibitor of Insect alpha-Amylase is a Major Allergen Associated with Baker's Asthma Disease. FEBS Lett. 248(1):119B122 (1989).
 49. Gomez, L.; Martin, E.; Hernandez, D.; et al.: Members of the alpha-Amylase Inhibitors Family from Wheat Endosperm are Major Allergens Associated with Baker's Asthma. FEBS Lett. 261(1):85B88 (1990).
 50. Baur, X.; Sauer, W.; Weiss, W.: Baking Additives as New Allergens in Baker's Asthma. Respiration 54:70B72 (1988).
 51. Blanco Carmona, J.G.; Juste Picon, S.; Garces Sotillos, M.: Occupational Asthma in Bakeries Caused by Sensitivity to alpha-Amylase. Allergy 46(4):274B276 (1991).
 52. Brisman, J.; Belin, L.: Clinical and Immunological Responses to Occupational Exposure to alpha-Amylase in the Baking Industry. Br. J. Ind. Med. 48:604B608 (1991).
 53. Quirce, S.; Cuevas, M.; Diez-Gomez, M.L.; et al.: Respiratory Allergy to Enzymes in Bakers' Asthma. J. Allergy Clin. Immunol. 90(6):970B978 (1992).
 54. Valdivieso, R.V.; Subiza, J.; Subiza, J.L.; et al.: Bakers' Asthma Caused by alpha-Amylase. Ann. Allergy 73:337B342 (1994).
 55. Fisher, A.: Hand Sermatitis C A "Baker's Dozen." Cutis 29(3):214B218 (1980).
 56. Fisher, A.: Allergic Bakers' Dermatitis Due to Benzoyl Peroxide. Cutis 43:128B129 (1989).
 57. Popa, V.; George, S.A.; Gavanescu, O.: Occupational

- and Nonoccupational Respiratory Allergy in Bakers. *Acta Allergol.* 25:159B177 (1970).
58. Schultze-Werninghaus, G.; Zachgo, W.; Rotermund, H.; et al.: *Tribolium Confusum* (Confused Flour Beetle, Rice Flour Beetle) C An Occupational Allergen in Bakers: Demonstration of IgE Antibodies. *Int. Arch. Allergy Appl. Immunol.* 94:371B372 (1991).
 59. Armentia, A.; Tapias, J.; Barber, D.; et al.: Sensitization to the Storage Mite *Lepidoglyphis destructor* in Wheat Flour Respiratory Allergy. *Ann. Allergy* 68:398B403 (1992).
 60. Tee, R.D.; Gordon, D.J.; VanHage-Hamsten, M.; et al.: Comparison of Allergic Responses to Dust Mites in U.K. Bakery Workers and Swedish Farmers. *Clin. Exp. Allergy* 22:233B239 (1992).
 61. Tee, R.D.; Gordon, D.J.; Crook, B.; et al.: Immune Response to Flour and Dust Mites in a United Kingdom Bakery. *Br. J. Ind. Med.* 49:581B587 (1992).
 62. Klaustermeyer, W.B.; Bardana, Jr., E.J.; Hale, F.C.: Pulmonary Hypersensitivity to *Alternaria* and *Aspergillus* in Baker's Asthma. *Clin. Allergy* 7:227B233 (1977).
 63. Kolopp-Sarda, M.N.; Massin, N.; Gobert, B.; et al.: Humoral Immune Responses of Workers Occupationally Exposed to Wheat Flour. *Am. J. Ind. Med.* 26:671B679 (1994).
 64. Herxheimer, H.: Skin Sensitivity to Flour in Bakers' Apprentices. *Lancet* 1(7481):83B84 (1967).
 65. Herxheimer, H.: The Skin Sensitivity to Flour of Bakers' Apprentices: A Final Report of a Long-Term Investigation. *Acta Allergol.* 28:42B49 (1973).
 66. Hartmann, A.; Wutrich, B.; Deflorin-Stolz, R.; et al.: Atopie-Screening: Prick Multitest, Gesamt-IgE Oder RAST. *Schweiz Med. Wochen.* 115:466B475 (1985).
 67. Awad el Karim, M.A.; Gad el Rab, M.O.; Omer, A.A.; el Haimi, Y.A.: Respiratory and Allergic Disorders in Workers Exposed to Grain and Flour Dusts. *Arch. Environ. Health* 41(5):297B301 (1986).
 68. Masalin, K.E.; Degerth, R.K.; Murtomaa, H.T.: Airborne Sugar and Flour Dust in the Finnish Confectionary Industry. *Appl. Ind. Hyg.* 3(8):231B235 (1994).
 69. Sandiford, C.P.; Nieuwenhuijsen, M.J.; Tee, R.D.; Taylor, A.J.N.: Determination of the Size of Airborne Flour Particles. *Allergy* 49:891B893 (1994).
 70. Massin, N.; Bohadana, A.B.; Wild, P.; et al.: Airway Responsiveness to Methacholine, Respiratory Symptoms, and Dust Exposure Levels in Grain and Flour Mill Workers in Eastern France. *Am. J. Ind. Med.* 27:859B869 (1995).
 71. Shamssain, M.: Respiratory Symptoms and Pulmonary Function in Flour Processing Workers in the Baking Industry. *Am. J. Ind. Med.* 27:359-365 (1995).
 72. Gimenez, C.; Fouad, K.; Cloudat, D.; et al.: Chronic and Acute Respiratory Effects Among Grain Mill Workers. *Int. Arch. Occup. Environ. Health* 67:311B315 (1995).
 73. Houba, R.; VanRun, P.; Heederick, D.; Doekes, G.: Wheat Antigen Exposure Assessment for Epidemiologic Studies in Bakeries Using Personal Dust Sampling and Inhibition ELISA. *Clin. Exp. Allergy* 26:154B163 (1996).
 74. Burstyn, I.; Teschke, K.; Kennedy, S.: Exposure Levels and Determinants of Inhalable Dust Exposure in Bakeries. *Ann. Occup. Hyg.* 41(6):609B624 (1997).
 75. Zuskin, E.; Kanceljak, B.; Schachter, E.; et al.: Respiratory Function and Immunological Status in Cocoa and Flour Processing Workers. *Am. J. Ind. Med.* 33:24B32 (1998).
 76. Houba, R.; Heederik, D.; Doekes, G.: Wheat Sensitization and Work-Related Symptoms in the Baking Industry are Preventable. An Epidemiologic Study. *Am. J. Respir. Crit. Care Med.* 158(5):1499B1503 (1998).